

A neuroanatomical framework for the central modulation of respiratory sensory processing and cough by the periaqueductal grey

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Abstract: Sensory information arising from the airways is processed in a distributed brain network that encodes for the discriminative and affective components of the resultant sensations. These higher brain networks in turn regulate descending motor control circuits that can both promote or suppress behavioural responses. Here we explore the existence of possible descending neural control pathways that regulate airway afferent processing in the brainstem, analogous to the endogenous descending analgesia system described for noxious somatosensation processing and placebo analgesia. A key component of this circuitry is the midbrain periaqueductal grey, a region of the brainstem recently highlighted for its altered activity in patients with chronic cough. Understanding the nature and plasticity of descending neural control may help identify novel central therapeutic targets to alleviate the neuronal hypersensitivity underpinning many symptoms of respiratory disease.

Keywords: Analgesia system; submedius nucleus; descending inhibition; airway afferents; respiratory sensation; vagal

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An overview of airway sensory processing in the brain

The airways and lungs are innervated by heterogeneous populations of sensory nerve fibers that respond to chemical and mechanical stimulation of the respiratory system (1). Many of these sensory nerve fibers are vagal in origin, derived from one of two distinct clusters of sensory neurons known as the nodose (or inferior) and jugular (or superior) vagal ganglia. In healthy airways, the activation of vagal sensory neurons evokes a wide range of respiratory responses and sensations that are important for the ongoing regulation of breathing, airway clearance and the maintenance of airway patency. These responses depend on well-defined reflex circuits integrated in the brainstem and less well-defined networks within the higher

brain. The latter represents an essential component of the more complex behavioral responses that accompany airway stimulation in health and disease occurring through ascending connections with subcortical and cortical brain regions or through the modulation of bulbar reflexes via descending control systems (2,3). In this brief review, we will focus on the higher brain circuits in receipt of airway sensory inputs, with a particular emphasis on a descending modulatory system involving the midbrain periaqueductal grey. This descending system is of interest because it may be capable of potentially regulating airway afferent nerve-mediated responses and recent evidence has demonstrated plasticity in descending control in patients with cough hypersensitivity (4). In exploring this topic, we will highlight possible central therapeutic targets for curtailing symptoms of pulmonary disease associated with excessive

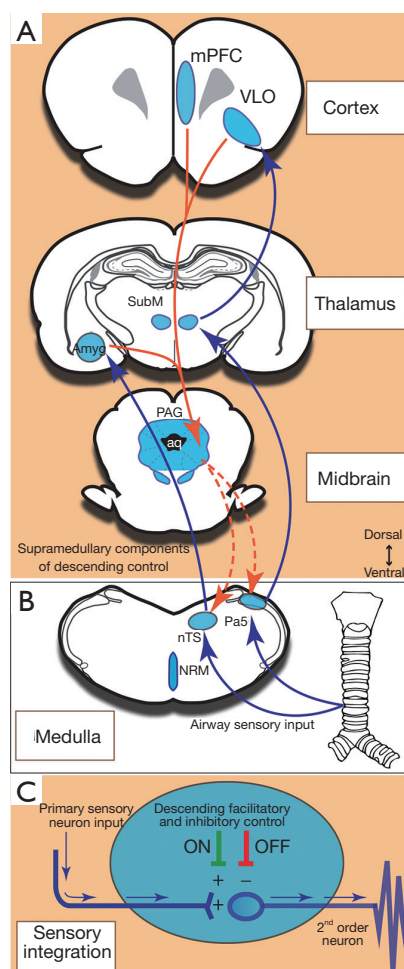


Figure 1 The core network putatively involved in descending regulation of airway sensory processing. The simplified schematic diagram shown in (A,B) depicts established (solid arrows) and likely (dashed arrows) neuronal connections which have been described in the rodent brain and may contribute to descending control. The medial prefrontal cortex (mPFC), the ventrolateral orbital cortex (VLO) and amygdala (Amyg) send descending (orange) projections to the midbrain periaqueductal grey (PAG). Outputs from the periaqueductal grey may either directly or indirectly (via the nucleus raphe magus (NRM) of the rostral ventromedial medulla) terminate in the nucleus of the solitary tract (nTS) and paratrigeminal nucleus (Pa5), where they can either inhibit (“OFF”, red) or facilitate (“ON”, green) processing between airway primary afferent terminals and recipient second order neurons (C). One mechanism by which descending control can be engaged is via activation of the submedial nucleus of the thalamus (SubM) which indirectly receives ascending (blue) inputs from the airways, predominately relayed via the medullary paratrigeminal nucleus (through pontine nuclei, not shown). The submedial nucleus has strong connectivity with the prefrontal cortical nuclei that govern descending control. See text for detailed information on circuit anatomy and neuropharmacology.

sensory nerve activity and propose neural mechanisms that might contribute to, or be targets for, inappropriate cough control.

Airway sensory inputs reach the higher brain via multiple ascending circuits. In rodents, at least two ascending pathways have been described. The first is specific for nodose ganglia-derived afferent fibers that synapse in the medullary nucleus of the solitary tract from which projections are sent to pontine and midbrain nuclei (e.g., lateral parabrachial nucleus and locus coeruleus), the hypothalamus (especially the paraventricular nucleus and lateral hypothalamic area), zona incerta, thalamus (mediodorsal and ventral posteromedial nuclei) and limbic brain (amygdala, insula and cingulate cortex) (5). The second ascending pathway is specific for jugular ganglia-derived afferent fibers, which terminate in the medullary paratrigeminal and trigeminal nuclei (rather than the nucleus of the solitary tract) from which ascending projections are sent extensively throughout central somatosensory processing networks including to the thalamus (ventral posterolateral and submedial nuclei) and somatosensory cortices (5). Consistent with this, functional brain imaging studies in humans have demonstrated that multiple central networks process the sensory (stimulus location, intensity and perception) and affective (degree of unpleasantness and emotional valencies) dimensions resultant from airway irritant stimulation (6,7). Whether these circuits in humans originate from distinct afferent neuron subsets innervating the airways, as they do in rodents, is not known. Regardless, these circuits presumably act in concert to promote motor behaviors (like coughing) that help to remove the initiating stimulus and relieve the sensory drive. Superimposed on these core sensorimotor circuits are several brain systems capable of modulating airway sensory processing and/or the resultant motor responses (6-8). This system includes network components that can suppress or facilitate sensorimotor processing (*Figure 1*) involving the prefrontal cortex (involved in placebo modulation of sensation), the insula cortex and inferior frontal gyrus (part of a fronto paralimbic system needed for motor response inhibition) and midbrain nuclei such as the periaqueductal grey (part of descending control).

In pulmonary disease, the excessive activation of airway sensory neural pathways is thought to contribute to the development of cough hypersensitivity syndrome, bronchospasm, excessive mucous secretion and the development of unpleasant pulmonary sensations, such as dyspnea and the persistent urge-to-cough. Accordingly, understanding the

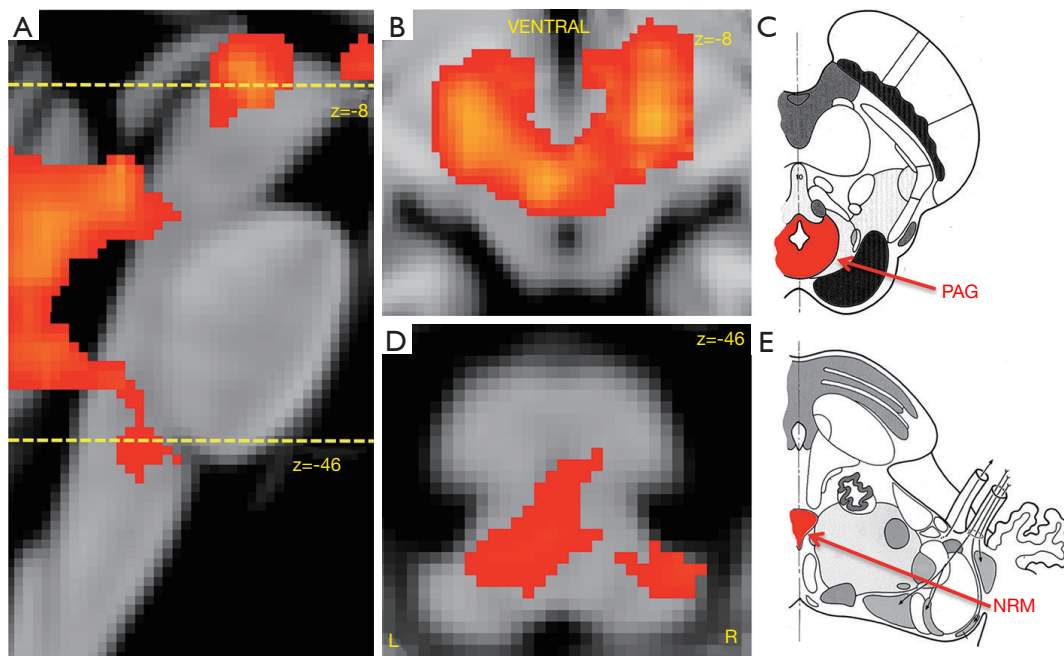


Figure 2 Functional brain imaging of bulbar descending control circuits in humans. (A) Regions showing blood oxygen level-dependent signal increases during inhalation of capsaicin in a cohort of healthy people are represented in red-yellow. The segment within the panel is a sagittal slice at the midline that includes the caudal to rostral extent of the brainstem. Dotted lines indicate the levels of the two axial slices shown in neighbouring panels. The “z” values are distances in mm inferior to the anterior commissure; (B) capsaicin inhalation activation occurs in the midbrain. The aqueduct is at the midline and is nearer the dorsal surface of the midbrain. Activation extends into a region ventral to the aqueduct; (C) a sketch of midbrain structures indicates in the red the spatial extent of the periaqueductal grey (PAG); (D) a slice through the rostral medulla shows capsaicin inhalation activation in this region; (E) activation seen in (D) is likely to encompass the nucleus raphe magnus (NRM) shaded in red on this sketch of the rostral medulla.

processes that induce and maintain sensitization should provide a sensible therapeutic pathway for symptom resolution. To this end, many studies have focused on the peripheral inflammatory mediators that are capable of promoting the activation of airway sensors (1). Less attention has focused on the central processes that might contribute to altered sensory neural responses (9). In animal models, pulmonary infections and cigarette smoke exposure enhance synaptic activity between primary sensory neurons and second order neurons in the nucleus of the solitary tract, a phenomenon that has been likened to central sensitization in the spinal cord following inflammatory or neuropathic pain states (9,10). Alternatively, functional brain imaging studies performed in chronic cough patients suggest that enhanced cough sensitivity may coincide with altered neural processing in the networks purported to be involved in modulating sensorimotor processing (4). In particular, activations in the midbrain regions containing the periaqueductal grey and adjacent nucleus cuneiformis are upregulated in cough patients (compared to healthy controls; *Figure 2*) during the

inhalation of irritant stimuli (4). Similar activations are also revealed in conditions of pain hypersensitivity (11). This raises important questions about the role of midbrain processing in the modulation of sensory sensitivity in disease conditions associated with both up and down-regulation of cough control. .

Descending control of sensory processing: the periaqueductal grey and pain

A well described endogenous neural system exists that is capable of modulating primary afferent inputs to second order neurons at the level of the spinal dorsal horn. Often referred to as the ‘analgesia system’ because of its opioid dependent capacity to suppress pain processing, this complex neural network can in fact both suppress and facilitate afferent processing depending on the specific neuronal components recruited. Central to this network is the midbrain periaqueductal grey, which serves to integrate information from multiple (spinal, bulbar and

cortical) sources and actuate the modulation of nociceptive processing through neural circuits that exert effects at the level of the spinal dorsal horn.

Stimulation of the periaqueductal grey with opioids or electrical currents evokes profound analgesia in a variety of species (12-18), and deep brain stimulation of the periaqueductal grey has been used therapeutically in patients with intractable pain (19). The periaqueductal grey receives nociceptive inputs from the spinal cord, likely through the parabrachial nucleus (20), and is also subject to descending influences from the cortex and other brain regions. Projections from the periaqueductal grey are widely distributed throughout the hindbrain, notably to pontine and medullary noradrenergic nuclei and the rostral ventromedial medulla, which likely represent the final neural pathways for dorsal horn modulation of nociceptive processing (21). Electrophysiological recordings of neurons in both the periaqueductal grey and rostral ventromedial medulla demonstrate distinct populations of cells defined as either activated or inhibited during the application of peripheral noxious stimuli, appropriately named "ON" and "OFF" cells, respectively. ON cells are presumed to facilitate noxious processing in the spinal cord, while the OFF cells are believed crucial components of the descending inhibitory system because their activity correlates with an inhibition of nociceptive sensory transmission (22,23). Facilitation and suppression are brought about by serotonergic and noradrenergic inputs to primary afferent terminals or dorsal horn interneurons in the spinal cord. The activity of ON cells in both the periaqueductal grey and rostral ventromedial medulla are inhibited by opioidergic inputs whereas OFF cell activity is disinhibited by opioid-dependent inhibition of GABAergic inhibitory inputs. Thus, opioids promote descending inhibition leading to analgesia (24-26). The capacity to facilitate or inhibit sensory processing presumably allows behavioral responses to noxious stimulation to be matched with competing demands (27).

The periaqueductal grey and vagal sensory processing

Conditions of hyperalgesia are associated with an imbalance of inhibitory and facilitatory descending inputs to the spinal cord, effectively reducing the capacity to invoke descending inhibition (28-31). In a functional brain imaging study, we noted that patients with chronic cough displayed increased neural activity in the periaqueductal grey and neighboring

nucleus cuneiformis, regions that are similarly activated during pain hypersensitivity (4) (*Figure 2*). This raises the question of whether vagal afferent processing from the airways is similarly subject to descending modulation from the midbrain periaqueductal grey and associated regions, and whether dysfunction in this system is an important component of cough hypersensitivity. However, airway vagal afferents of course terminate in both the medullary nucleus of the solitary tract and paratrigeminal nucleus (and not the spinal dorsal horn) and as such, it is important to consider whether the periaqueductal grey and/ or rostroventral medial medulla provide functional inputs to these medullary sensory processing nuclei.

The periaqueductal grey has been repeatedly shown to play a role in both respiratory and cardiovascular control, the nature of which depends on the specific subregion under study. For example, both electrical and chemical stimulation in the ventrolateral periaqueductal grey elicit hypotension, vagal bradycardia and facilitate the baroreflex, whereas stimulation in the dorsal region has the opposite effect (32-34). Chemical activation of the dorsolateral periaqueductal grey in rats increases respiratory rate and overall respiratory activity (35,36) and the respiratory effects elicited from the dorsal periaqueductal grey are more prominent from the caudal end of the nucleus, suggesting a rostrocaudal, as well as the dorsoventral, organization (37). However, it is unclear if such effects are mediated by the modulation of medullary sensory processing or through direct influences of premotor neurons in the rostral ventrolateral medullary cardio-respiratory groups. Anatomical tracing studies have demonstrated direct projections from the ventrolateral periaqueductal grey and rostral ventromedial medulla to the nucleus of the solitary tract (38-40), providing an anatomical framework for modulatory control (*Figure 1*). Functional evidence for descending modulation of vagal afferent processing was demonstrated in an elegant study by Sessle *et al.* (41) in which stimulation of the cat periaqueductal grey or the nucleus raphe magnus (part of the rostral ventromedial medullary group involved in nociceptive control) significantly inhibited respiration and suppressed vagally-mediated reflex cough and swallow, coinciding with a marked suppression of neuronal activity in the nucleus of the solitary tract. Furthermore, they demonstrated that responses were reversed by the mu-opioid receptor antagonist naloxone, consistent with an activation of the antinociceptive system. Remarkably, stimulation of the periaqueductal grey and raphe magnus in the same animals

also inhibited the nociceptive jaw-opening reflex elicited by noxious tooth pulp stimulation, suggesting commonalities between the inhibitory regulation of pain and upper airway sensory evoked responses. Whether descending facilitation can be evoked at the level of the nucleus of the solitary tract was not assessed.

Only recently was it discovered that a population of airway afferents project to the medullary paratrigeminal nucleus (5,42-44) and consequently the possibility of descending modulation of paratrigeminal vagal afferent processing has not been studied. Nevertheless, the periaqueductal grey and the nucleus raphe magnus are important for modulation of trigeminal afferent processing throughout the spinal trigeminal system. For example, electrical stimulation of the periaqueductal grey and nucleus raphe magnus (a component of the rostral ventromedial medulla) inhibited all types of neurons within the trigeminal medullary dorsal horn (45,46) as well as tooth pulp afferent processing within the spinal trigeminal nucleus (47,48). Neuronal responses in the trigeminal oralis region evoked by tooth pulp stimulation were suppressed by both periaqueductal grey and nucleus raphe magnus conditioning stimuli and given that such responses are naloxone-sensitive (49) it is consistent with the activation of the descending antinociceptive system.

Thalamic and cortical regulation of descending control: 'top-down' modulation

Descending modulation of sensory processing is clearly well defined, but this raises the question 'what regulates the periaqueductal grey to drive this descending control'? Although graded sensory stimuli generally result in graded responses (action potentials) in the primary sensory neurons detecting that stimulus, the level of sensation experienced may not correlate with stimulus intensity. Indeed, sensory perception is subject to significant higher brain modulation dependent upon past experiences, stress and anxiety, attention and other complex cognitive processes, and this likely occurs through 'top-down' neural pathways arising from the prefrontal cortex and capable of modulating neuronal activity in the midbrain periaqueductal grey (*Figure 1*).

Studies in both animals and humans have demonstrated the existence of several prefrontal cortical inputs to periaqueductal grey neurons, including from neurons originating in the rostral agranular insula cortex (a small area of cerebral cortex positioned above the rhinal fissure in rodents defined by the absence of cortical layer four), the neighbouring ventrolateral orbital cortex (again adjacent to

the rhinal fissure in rodents), as well as from the dorsolateral prefrontal cortex in humans (the medial prefrontal cortex is the homologue in rodents) (50-53). Antinociception can be readily evoked by prefrontal cortex stimulation in rodents, and this is prevented by prior inhibition or lesioning of the ventrolateral periaqueductal grey (54), suggesting that neurons in the periaqueductal grey are central to the prefrontal descending modulation of pain. Transcranial magnetic stimulation of the dorsolateral prefrontal cortex in humans similarly reduces noxious sensations (55) and anatomical tracing studies in rodents confirm the output connectivity of the prefrontal cortex to the periaqueductal grey (56,57).

Prefrontal cortical neurons involved in pain modulation, in turn, receive inputs from a wide variety of central sources. One mechanism of prefrontal cortical regulation involves afferent information being relayed from the spinal dorsal horn to the cortex via an obscure collection of sensory processing neurons in the thalamus known as the submedial nucleus (*Figure 1*). Best defined in the rats, the submedial nucleus is located close the cerebral midline, ventral to the central medial thalamic nucleus and dorsal to the paraventricular nucleus of the hypothalamus. It is populated by output neurons and local interneurons responsive to noxious stimuli from the viscera, muscles and skin (58-60) and it receives direct nociceptive inputs from neurons in laminar one of the trigeminal nucleus and spinal dorsal horn (61-63). Output neurons of the submedial nucleus project heavily to the prefrontal cortex, including the rostral agranular insula and the ventrolateral orbital cortices. As submedial output neurons are principally glutamatergic in nature, they provide excitatory drive to recipient cortical neurons (64).

The neuropharmacology of these thalamocortical loops has been studied in some detail. The nociceptive-related inputs to the submedial nucleus and prefrontal cortex increases the activity of the output neurons, both directly via the release of glutamate and indirectly by enkephalins that reduce the activity of the local tonically inhibitory GABAergic interneurons, resulting in a net increase in the activity of both submedial nucleus and the recipient cortical neurons (65). This activation pattern can be mimicked by electrical stimulation or exogenously administered glutamate or opioid agonists into either the submedial nucleus or the prefrontal cortex, resulting in a suppression of the behavioral responses to nociception (54,64,66,67). Further functional assessment of the connections showed that inhibiting the prefrontal cortex suppresses the behavioral effects produced

by stimulating the submedial nucleus (64), and paradoxically enhanced nociceptive responses consistent with the notion that there is ongoing tonic activity in the descending control network (68). This tonic activity may reflect additional inputs to the submedial nucleus from the raphe (serotonergic) and the reticular thalamus (GABAergic) which provide alternative sources of excitatory and inhibitory (respectively) influence over submedial output neurons, while prefrontal cortical output neuronal activity is facilitated by inputs from raphe (serotonergic) and the ventral tegmental area (dopaminergic) (53,69,70).

'Top down' control of visceral sensory processing

There is evidence to suggest that both the prefrontal cortex and submedial nucleus of the thalamus play a role in the regulation of visceral noxious sensory processing. In this regard, the evidence is perhaps strongest for spinal visceral nociceptive pathways, although some evidence also exists for bulbar visceral afferent pathways. In a model of acute visceral pain, both colorectal distension and noxious somatic stimulation (but not innocuous stimuli) modulated the activity of the same neurons in the ventrolateral orbital cortex and submedial nucleus (71-75), indicating that viscerosomatic sensory convergence was common in the nociceptive control system. Furthermore, administration of intravenous morphine dose-dependently attenuated descending control evoked by noxious visceral stimulation similar to the role that opioidergic pathways play in somatic nociception. Electrical stimulation of the submedial nucleus resulted in intensity dependent attenuation of colorectal distension evoked behavioral responses (75,76), while electrical or chemical stimulation (glutamate) of the periaqueductal grey or the rostral ventromedial medulla inhibited the majority of spinal cord neurons activated by colorectal distension in the rat (77,78). Taken together, these data suggest a role of the thalamo-cortico-bulbar descending pathway in the regulation of visceral nociception.

With respect to vagal afferents, vagus nerve stimulation in the cat induced activity in orbital cortex neurons that were also responsive to cutaneous stimuli (79). Consistent with this, electrical stimulation of the orbital gyrus in anesthetized cats acutely suppressed cough evoked by activation of the superior laryngeal nerve (80) whereas electrolytic lesions of the orbital region enhanced the hypoxic ventilator response, albeit not in all animals studied (81). In humans, placebo conditioning substantially reduces the

perception of the urge-to-cough associated with inhaled airway irritants, and the magnitude of this inhibition correlates with the degree of activation in the dorsolateral prefrontal cortex (82), comparable to placebo analgesia. Recently, we used transsynaptic anterograde viral tracers in rats to provide anatomical evidence for airway-specific vagal afferent inputs to the submedial nucleus, ventrolateral orbital cortex and medial prefrontal cortex (42-44) suggesting that vagal afferents might similarly modulate thalamo-cortical inputs to the midbrain (*Figure 1*). In a follow up study, using a genetically modified conditional transsynaptic viral tracing system, we reported that only the airway vagal afferents passing through the paratrigeminal nucleus in the brainstem (i.e., jugular vagal afferents) contributed to this thalamo-cortical circuit (5). Both the submedial nucleus and the ventrolateral orbital cortex were devoid of inputs via the nodose ganglia and the nucleus of the solitary tract.

Inputs from the amygdala represent an alternative pathway for regulating the activity of periaqueductal grey-mediated descending control (*Figure 1*). Thus, electrical stimulation of the medial or central amygdala elicits antinociception which is inhibited by blockade of the periaqueductal grey (83), indicative of amygdala-evoked nociceptive control during fear and other aversive states. In this regard, it is interesting that ascending vagal sensory inputs from the airways are relayed extensively to the central nucleus of the amygdala (5,42), perhaps representing an alternative control loop for eliciting descending modulation of vagal sensory processing.

Clinical significance and concluding remarks

The central integration that culminates in generating a respiratory sensation and modulating a respiratory behavior is complex in nature. Many respiratory behaviors are not simply reflexes, but are subject to significant regulation by higher brain processes. Human studies using functional brain imaging have identified forebrain and bulbar response patterns that are consistent with descending control of airway sensory processes (6,84), and animal studies have begun to identify their anatomical connectivity with airway sensory pathways (5,43). Whether these circuits are altered in disease remains largely unstudied and whether they are ultimately targetable from a therapeutic standpoint to relieve the symptoms of disease remains to be seen. For example, cough can be both up-regulated (for example in pulmonary disease) and down-regulated (in neurological

conditions such as Parkinson's disease) and it is tempting to speculate that modulation of either the inhibitory or facilitatory descending control networks might provide a therapeutic option for normalising cough in these conditions. Indeed, opioid therapy is the current gold-standard antitussive agent, and likely suppresses cough due to an action within the descending inhibitory control systems of the brain. Additionally, altered activity within the periaqueductal grey and related nuclei accompanies chronic cough (4) and this could conceivably either contribute to the establishment of up-regulated cough states (i.e., enhanced facilitation) or represent the recruitment of descending control mechanisms as a compensatory strategy in an attempt to dampen disordered coughing (i.e., enhanced inhibition). Whether similar plasticity occurs in these networks in conditions of down-regulated cough is not known. Accordingly, a deeper understanding of the role of descending control in disordered cough states is warranted as this may afford novel opportunities for regulating disordered cough in a myriad of diseases.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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